Original Research Article

Association of Tranexamic acid with GCS in patients with traumatic brain injury.

Abstract:

Background:

Traumatic Brain Injury (TBI) occurs due to head injury ranging from simple blow to penetrating injury. TBI refers to a violently produced brain damage that is either blunt or piercing, or accelerates or decelerates, resulting in the development of various clinical signs and symptoms such as loss of consciousness or lowered awareness level, entire or partial loss of memory, and various neurological or neuropsychological abnormalities, all of which can lead to disability or death. The aim of current study was to determine the effect of Tranexamic acid on GCS score in TBI patients. As a result, antifibrinolytic drugs like tranexamic acid (TXA) may help to prevent traumatic ICH.

Methodology:

In this Quasi experimental type of study the 126 patients were recruited from the emergency department of Ziauddin University and Hospital North site who were presented with the traumatic brain injury. Confirmed patients of TBI were distributed into two groups; **Tranexamic acid Group:** A group of TBI patient received 1 gm. of tranexamic acid infused over ten minutes within three hours of injury along with standard treatment and **Placebo Group:** A group of TBI patient will only received standard treatment.

Results:

Comment [Ma1]: when abbreviation is given first time, you shoud write full name

The mean age of the study subjects was found to be 45.6±18.7 ranged between 18 to 89 years. While assessing the clinical parameters mean temp recorded is 36.6 ºC, with mean respiratory rate and pulse rate of 20.3 and 91.6 respectively. The comparative analysis of the two treatments groups in which one group got the TXA and other had the usual recommended drugs only with the effectiveness of TXA in term of improvement of GCS showed highly significant statistical association.

Conclusion:

Use of Trenaxamic acid (TXA) helps in improvement of GCS at many intervals of 6 hours, 12 hours and 24 hours as compared to those who received conventional treatment.

Keywords : Tranexamic acid, GCS, Traumatic, Hematoma, Injury

Comment [Ma2]: is it a result of the study? should be placed in Methodology

Comment [Ma3]: Improvement or the scale? maybe scores?

Introduction

Traumatic Brain Injury (TBI) occurs due to head injury ranging from simple blow to penetrating injury. (1) TBI refers to a violently produced brain damage that is either blunt or piercing, or accelerates or decelerates, resulting in the development of various clinical signs and symptoms such as loss of consciousness or lowered awareness level, entire or partial loss of memory, and various neurological or neuropsychological abnormalities, all of which can lead to disability or death. TBI is regarded as a major public health issue that not only affects the global population but also causes socioeconomic issues. (2-5) TBI incidence is increasing annually, according to the World Health Organization (WHO), as is the rate of disability and mortality. TBI can result in permanent or temporary brain impairment, limiting social and practical tasks and lowering quality of life. (6) TBI that lasts for a long time might lead to depression and other chronic illnesses. A recent study on global incidence of traumatic brain injury by Dewan MC, et

al. reported that approximately 69 million cases of TBI are reported annually around the world of which road traffic accidents (RTAs) and falls are the most commonly reported. (7) Prevalence of RTAs was high in South East Asia (56%) and Africa (56%) and RTAs was low in North America (25%). (8) Incidence of road traffic injuries (RTI) were high 1.5% in Southeast Asia followed by Europe with incidence of 1.2%. Overall global incidence of TBI was 939 cases in 0.1 million people (69 million/year), whereas incidence of mild TBI was 740 cases in 0.1 million people (55.9 million/year) and the incidence of severe TBI was 73 cases in 0.1 million people (5.48 million/year). (9) 274,436 patients in emergency department of different hospital of Pakistan and reported traumatic brain injury in 12,125 (4.4%) patients. (10) Intracranial bleeding is one of the most common and severe complication of brain injury that not only increases the risk of disability but also increases the risk of mortality. (11) Bleeding can start immediately after injury and can persists for several hours. Intracranial bleeding increases the intracranial pressure leading towards brain herniation and ultimately death. (12) An initial coma score evaluation is done using the Glasgow Coma Scale (GCS) which was developed in the year 1974 by two neurosurgeons at the University of Glasgow (Teasdale and Jannet). (13) It is the most commonly used tool for assessment of consciousness. GCS was categorized into three parameters for evaluation of consciousness including; eye, verbal and motor response. GCS has a score ranging from 3-15, three for worst and 15 for best. TBI is categorized into following three types on the basis of GCS score; mild TBI with GCS score 14-15, moderate TBI with GCS score 9-13 and severe TBI with GCS score 3-8. (14-16)

Comment [Ma4]: when?

Methodology:

The aim of current study was to determine the effect of Tranexamic acid on GCS score in TBI patients. In this Quasi experimental type of study the 126 patients were recruited from the emergency department of Ziauddin University and Hospital North site who were presented with the traumatic brain injury. All the adult patients aged 18 and above with between GCS 3 and 12 with evident of intracranial hemorrhage were included by using consecutive sampling technique after taking the approval from Ethics Review Committee (ERC) of Zia Uddin University Karachi accordance with institutional guidelines (3070121KZEM). Demographic details (such as name, gender, age), presenting complains and medical history of each patient was obtained from patient's family. Each patient was triaged, evaluated for vital signs including temperature, pulse, BP and RR. In other words a primary survey followed by a secondary survey was performed. The GCS was evaluated, patient was stabilized. The patient underwent an urgent CT brain.

Confirmed patients of TBI were distributed into following two groups;

1. **Tranexamic acid Group:** A group of TBI patient received 1 gm. of tranexamic acid infused over ten minutes within three hours of injury along with standard treatment.
2. **Placebo Group:** A group of TBI patient will only received standard treatment.

Patients of both groups were evaluated for GCS at 6 hours, 12 hours and then twenty-four hours after of administration of tranexamic acid and standard treatment. There was no risk involved in this study as well as no any risk of drug reactions. Adverse effects and as far as management of allergic responses of the drug is concerned, such patients were treated with immediate discontinuation of the drug, followed by applying the anaphylaxis protocol like starting steroids, anti-allergic medications, strict monitoring of vitals, securing the airway if needed, fluids to build up the patient's hydration.

Results:

The mean age of the study subjects was found to be 45.6±18.7 ranged between 18 to 89 years. While assessing the clinical parameters mean temp recorded is 36.6 ºC, with mean respiratory rate and pulse rate of 20.3 and 91.6 respectively. Mean systolic blood pressure recorded was 143.3mmHg and systolic blood pressure was 84.9mmHg. Mean GCS at time of presentation in emergency department, after 6 hour, 12 hours and 24 hours are calculated as 10.71, 10.78, 10.95 and 11.06 respectively that showed the significant improvement of GCS with time. Table: 1

Table: 1 Means of study parameters in all study subjects

Parameter	Mean	Minimum	Maximum
Age	45.6 Years	18 Years	89 Years
Temperature	36.6 ºC	36 ºC	39 ºC
Systolic BP	143.3mmHg	60mmHg	260mmHg
Diastolic BP	84.9mmHg	40mmHg	197mmHg
Respiratory Rate	20.3/Min	12/Min	24/Min
Pulse Rate	91.6/Min	58/Min	156/Min

The study included 91 (72.2 percent) males and 35 (27.8%) females. For statistical purposes, we split the patients into three age groups: 18 to 40 years, 41 to 60 years, and > 60 years, and found that the majority of the patients were in the 41 to 60 year age group (52/126: 41.3 percent), followed by the 18 to 40 year age group. We also discovered that a high number of patients (70/126: 55.6%) had TBI as a result of road traffic accidents (RTA) and unintentional falls (54/126: 42.9%), while the rest had TBI as a result of other causes such as attack or conflict. We also graded all of the patients' severity based on their clinical characteristics and radiological results. The majority of patients (93/126: 73.8%) had a moderate TBI, while 33/126: 26.2%) had a severe damage. None of them had shown up with a minor injury. Figure 1, 2 and 3

Comment [Ma5]: what kimnd of attack (animal, human?)

Comment [Ma6]: patients severity? or TBI severity?

Figure:1 Frequency of study subjects according to Gender

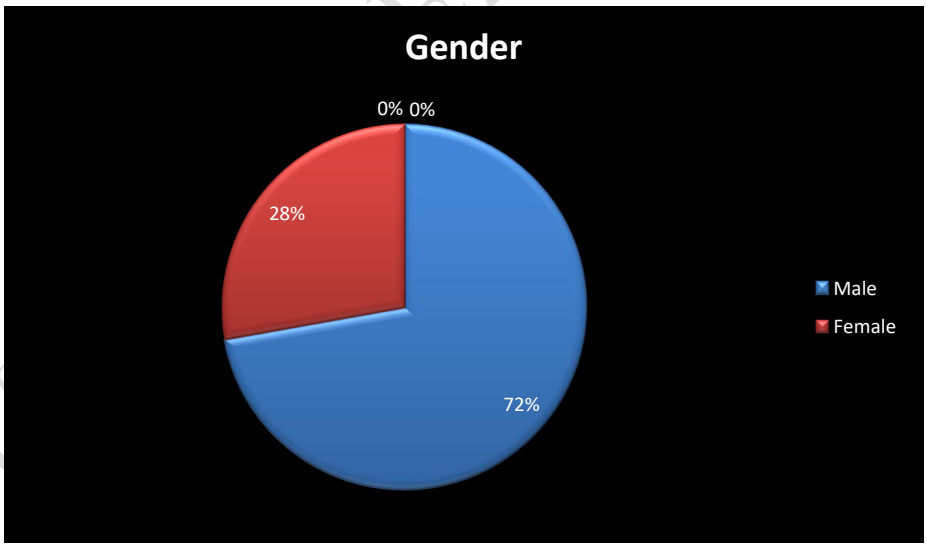


Figure: 2 Frequency of cause of injury

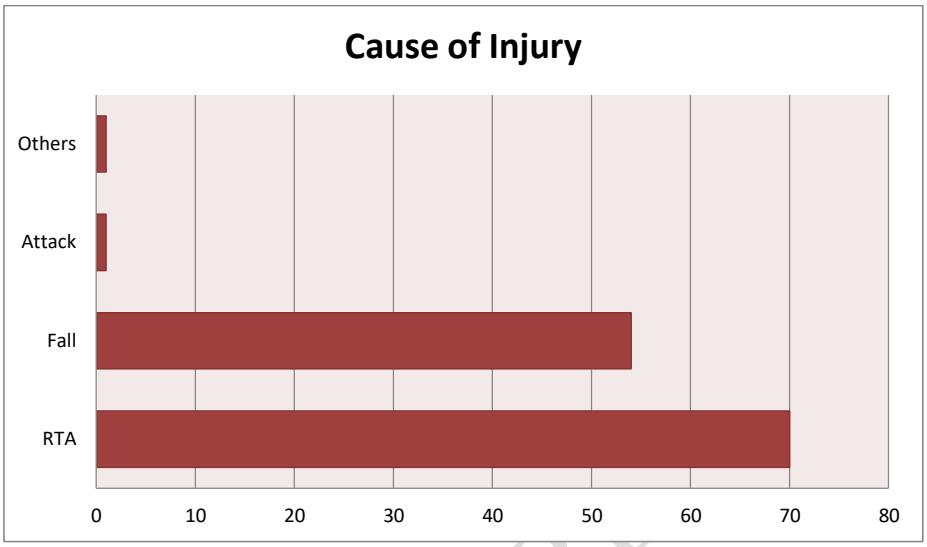
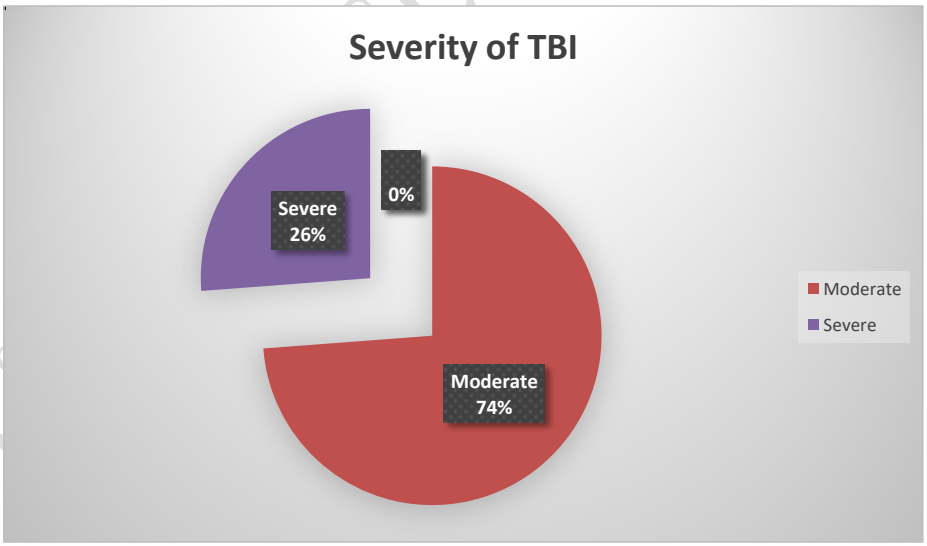


Figure: 3 Severity of Traumatic brain injuries



The comparative analysis of the two treatments groups in which one group got the TXA and other had the usual recommended drugs only with the effectiveness of TXA in term of improvement of GCS showed highly significant statistical association with p value: 0.00. Table: 2. Furthermore we also determined the link between the association of the effectiveness with improvement of GCS score after some intervals of 6 hours, 12 hours and 24 hours. Each and every time interval had highly significant association p-values showed in Table: 3.

Comment [Ma7]: Scale can not be improved, scores may be higher or lower

Table: 2. Association of effectiveness with treatment groups

Effectiveness	Group		p-value
	TXA	Placebo	
GCS Improved	42	10	0.00*
GCS Not Improved	7	67	

*Fisher's Exact Test

Table: 3. Statistical link of effectiveness with GCS at different intervals

GCS Improvement	GCS Interval	p-value
Effectiveness	At arrival	0.002[c]
	After 6 hours	0.007[c]
	After 12 hours	0.006[c]
	After 24 hours	0.000[c]

[c]Independent sample T-test

Discussion:

TBI is the leading cause of death and disability in the World. TBI-related intracranial hemorrhage (ICH) is linked to a high risk of coagulopathy, which increases the risk of hemorrhage growth and increases the mortality rate. (17) As a result, antifibrinolytic drugs like tranexamic acid (TXA) may help to prevent traumatic ICH. The purpose of this study was to see

how much ICH grew after TA was administered to TBI patients. Short courses of tranexamic acid (TXA) have been shown to minimize rebleeding in spontaneous intracranial haemorrhage and to reduce bleeding in elective surgery. (2) In TBI patients, the safety of early short-course TXA care was consistent with no increased risk of non-fatal vascular occlusive incidents with early short-course TXA treatment in traumatic bleeding patients. (18) In present study we also found a significant improvement of GCS score measured at different of 6 hour, 12 hours and 24 hours after presenting in the emergency department. Same findings were also found by Abolfazl et al in his randomized clinical trial in 2017 and others. In present research the mean age was found 45.6 years that is line with the other studies who found the same results. (10, 19) Age remained a mainstay of discussion for long time time as some primary traumatic brain injuries are common in old ages and some are more common in youngers. Primary brain injury in our study population is common in middle aged persons followed by young adults due to different causative agents as road traffic accident (RTA) are more evident in this age group and in our analysis majority of the study participants had TBI secondary to RTA and fall. Male were predominant in present study as compared to female due to different exposure of risk factors and trends in our population. RTAs are more evident and common in males in our areas on account of less number of female drivers. (20) In current study we found that most of patients presented with TBI have GCS between 10 to 11 irrespective of cause and age. In many researches have different GCS scores that may be due to many factors like old age have poor GCS because of low understanding of language and obeying command. (21) The Glasgow Coma Scale (GCS), a scoring system never intended to classify brain injury per se but rather level of consciousness, has historically been used to classify traumatic brain injury as mild, moderate, or extreme.(13) While the GCS can be helpful in the clinical management and prognosis of TBI, it "does not

Comment [Ma8]: their

Comment [Ma9]: cause of what?

Comment [Ma10]: who gahe scores?

include clear details about the pathophysiologic processes that are responsible for the neurologic defects and targeted by therapies," according to a TBI consensus workgroup. We also found that use of TXA or fibrinolytics in TBI helps in improvement of patient in term of consciousness (GCS). Many researches support this as they have positive results after use of fibrinolytic agents. (22, 23) While fibrinolytic assays are not commonly used to diagnose posttraumatic coagulopathy, circulating biomarkers such as D-dimer and fibrin degradation products have shown promise in predicting outcome. Early tranexamic acid administration in patients with TBI and reported hyperfibrinolysis has been suggested as a way to enhance clinical results even further. (22) The current research supports the use of tranexamic acid as an empiric treatment for severe trauma haemorrhage.

Comment [Ma11]: what kind of results?

Conclusion:

Traumatic brain injury is more evident in male at second decade of life. RTA followed by fall is the more common cause. Patients presented in emergency department have moderate traumatic brain injury with mean GCS of 10. Severe traumatic brain injury is also reported with low GCS. All of the patients have associated intracerabral hemorrhage in both cases. Use of Trenaxamic acid (TXA) helps in improvement of GCS at many intervals of 6 hours, 12 hours and 24 hours as compared to those who received conventional treatment.

Comment [Ma12]: what about female?

Comment [Ma13]: followd by or because of

Comment [Ma14]: Figure 2????????

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

1. Callahan ML, Lim MM. Sensory sensitivity in TBI: Implications for chronic disability. Current Neurology and Neuroscience Reports. 2018;18(9):1-8.
2. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. The Medical clinics of North America. 2020;104(2):213-38.
3. van Dijck JT, van Essen TA, Dijkman MD, Mostert CQ, Polinder S, Peul WC, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? Acta neurochirurgica. 2019;161(5):875-84.
4. Voormolen DC, Haagsma JA, Polinder S, Maas AI, Steyerberg EW, Vuleković P, et al. Post-concussion symptoms in complicated vs. uncomplicated mild traumatic brain injury patients at three and six months post-injury: results from the CENTER-TBI study. Journal of clinical medicine. 2019;8(11):1921.
5. Wijayatilake DS, Sherren PB, Jigajinni SV. Systemic complications of traumatic brain injury. Current opinion in anaesthesiology. 2015;28(5):525-31.
6. Cipriano A, Pecori A, Bionda AE, Bardini M, Frassi F, Leoli F, et al. Intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: significant differences between direct oral anticoagulants and vitamin K antagonists. Internal and emergency medicine. 2018;13(7):1077-87.
7. DeGrauw X, Thurman D, Xu L, Kancherla V, DeGrauw T. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: An analysis of insurance claims data, 2004–2014. Epilepsy research. 2018;146:41-9.
8. Theadom A, Mahon S, Hume P, Starkey N, Barker-Collo S, Jones K, et al. Incidence of sports-related traumatic brain injury of all severities: a systematic review. Neuroepidemiology. 2020;54(2):192-9.
9. Dunne J, Quiñones-Ossa GA, Still EG, Suarez MN, González-Soto JA, Vera DS, et al. The epidemiology of traumatic brain injury due to traffic accidents in Latin America: a narrative review. Journal of neurosciences in rural practice. 2020;11(2):287.
10. Ashraf M, Kamboh UA, Zubair M, Sultan KA, Raza MA, Hussain SS, et al. Prevalence of anemia in pediatric patients of traumatic brain injury and problems associated with management in a developing country: Unfolding of an underrated comorbidity. Surgical Neurology International. 2021;12.
11. Azad A, Kang HP, Alluri RK, Vakhshori V, Kay HF, Ghiassi A. Epidemiological and treatment trends of distal radius fractures across multiple age groups. Journal of wrist surgery. 2019;8(4):305.
12. DeGeorge Jr BR, Van Houten HK, Mwangi R, Sangaralingham LR, Larson AN, Kakar S. Outcomes and complications in the management of distal radial fractures in the elderly. JBJS. 2020;102(1):37-44.
13. Ganti L, Stead T, Daneshvar Y, Bodhit AN, Pulvino C, Ayala SW, et al. GCS 15: when mild TBI isn't so mild. Neurological Research and Practice. 2019;1(1):1-8.
14. Saika A, Bansal S, Philip M, Devi BI, Shukla DP. Prognostic value of FOUR and GCS scores in determining mortality in patients with traumatic brain injury. Acta neurochirurgica. 2015;157(8):1323-8.

15. Study IB, Collaborators C-. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ (Clinical research ed). 2011;343:d3795.
16. Subaiya S, Roberts I, Komolafe E, Perel P. Predicting intracranial hemorrhage after traumatic brain injury in low and middle-income countries: a prognostic model based on a large, multi-center, international cohort. BMC emergency medicine. 2012;12(1):1-7.
17. Fair KA, Farrell DH, McCully BH, Rick EA, Dewey EN, Hilliard C, et al. Fibrinolytic activation in patients with progressive intracranial hemorrhage after traumatic brain injury. Journal of neurotrauma. 2021;38(8):960-6.
18. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC emergency medicine. 2013;13(1):1-7.
19. Levin HS, Temkin NR, Barber J, Nelson LD, Robertson C, Brennan J, et al. Association of Sex and Age With Mild Traumatic Brain Injury–Related Symptoms: A TRACK-TBI Study. JAMA network open. 2021;4(4):e213046-e.
20. Brennan PM, Murray GD, Teasdale GM. Simplifying the use of prognostic information in traumatic brain injury. Part 1: The GCS-Pupils score: an extended index of clinical severity. Journal of neurosurgery. 2018;128(6):1612-20.
21. Garza N, Toussi A, Wilson M, Shahlaie K, Martin R. The increasing age of TBI patients at a single level 1 trauma center and the discordance between GCS and CT Rotterdam scores in the elderly. Frontiers in neurology. 2020;11:112.
22. Anderson TN, Farrell DH, Rowell SE, editors. Fibrinolysis in Traumatic Brain Injury: Diagnosis, Management, and Clinical Considerations. Seminars in thrombosis and hemostasis; 2021: Thieme Medical Publishers, Inc.
23. Gall LS, Davenport RA. Fibrinolysis and antifibrinolytic treatment in the trauma patient. Current opinion in anaesthesiology. 2018;31(2):227-33.